Student summer research opportunity

Project title: Mechanistic Drivers of SLFN12-Mediated Chemotherapy Sensitization in Lung Adenocarcinoma

PI: Marc D. Basson, MD, PhD

Location: RGE 100

Abstract

The Basson Lab has been investigating the role of SLFN12, an intermediate member of the Schlafen protein family, in the biology and drug responsiveness of several cancer types. Prior work from the laboratory showed that high SLFN12 expression is associated with improved prognosis and increased chemotherapy sensitivity in cancers such as triple-negative breast cancer. Our ongoing research in lung adenocarcinoma has demonstrated similar trends, where SLFN12 overexpression enhances sensitivity to specific cytotoxic drugs in some cell lines. However, other lung adenocarcinoma cell lines remain resistant or display only minimal changes in drug response despite SLFN12 overexpression. To understand these differences, we analyzed proteomic profiles from SLFN12-overexpressing sensitive and resistant lung adenocarcinoma cell lines. Several proteins were significantly upregulated in the sensitive line compared with the resistant line, while other proteins were downregulated in the sensitive cells but elevated in the resistant ones. These findings suggest that downstream effectors of SLFN12 may determine whether a cell line becomes sensitized or remains resistant. We are generating stable lentiviral cell lines that either overexpress SLFN12 or contain an empty vector control in one sensitive and one resistant lung adenocarcinoma model. The proposed project will manipulate proteins identified from proteomic analysis by knocking down proteins that are upregulated in the sensitive line and overexpressing proteins that are downregulated. The goal is to determine whether altering these targets can convert sensitive lines into resistant ones and, conversely, make resistant lines more sensitive to chemotherapy.

Significance

This study will help define the molecular mechanisms that govern SLFN12-mediated chemotherapy sensitization in lung adenocarcinoma. By identifying and validating the key downstream proteins that distinguish sensitivity from resistance in SLFN12-overexpressing cells, the project may identify new biomarkers that predict chemotherapy response. These findings may also reveal new therapeutic targets that could be modulated to overcome drug resistance. A clearer understanding of how SLFN12 interacts with downstream pathways could ultimately contribute to developing more effective treatment strategies for lung adenocarcinoma patients.

Research methods that will be learned by the student

- Mammalian cell culture
- Lentiviral transduction and stable cell line maintenance
- Gene knockdown and gene overexpression methods

- Crystal violet cell viability assays
- Drug preparation and dose response curve generation
- Q PCR
- Western blotting
- Interpretation of proteomic data
- Data analysis

Proposed methods of data analysis: Standard statistical techniques, including t-tests and outlier analysis

How will the anticipated findings contribute to the success of the overall research?

If altering the expression of SLFN12-associated downstream proteins changes chemotherapy sensitivity, this will help confirm the pathways that regulate SLFN12's effect in lung adenocarcinoma. These results will support the development of predictive markers for chemotherapy responsiveness and may guide the design of therapeutic strategies that resensitize resistant tumors. Positive findings would justify additional validation in mouse models and could inform future translational efforts, including the preparation of an IND application for human studies.

Student fellow mentoring plan

The student will work with a trained member of the Basson laboratory, receiving daily guidance and support throughout the project. The students will also participate in weekly two-hour laboratory meetings focused on data presentation, experimental design, troubleshooting, and scientific discussion. Depending on the student's interest, there may be opportunities to engage in additional projects in the laboratory, including small animal work or clinical research initiatives within the Basson research group. The student will prepare a poster or oral presentation for the student research day under Dr. Basson's supervision, and the data generated may contribute to a manuscript on which the student will be a coauthor. All research activities will take place in the Basson laboratory.